an oligonucleotide having the sequence SEQ ID: 8 or an oligonculeotide primer at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 8 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 7;

(d) comparing the amount of the mRNA from step (c) to an amount of mRNA of an internal control.

REMARKS

Claims 6 and 17 have been amended. The language "at least about 80% identical" has been amended to "at least 80% identical." No new matter is added by this amendment to the subject application.

Rejection under 35 U.S.C. § 112, First Paragraph - Written Description

The Examiner has maintained the rejection of claims 6-11, 17-22, and 26 under 35 U.S.C. § 112, first paragraph, as allegedly encompassing subject matter lacking sufficient written description. The Examiner alleges that the specification discloses SEQ ID Nos: 1, 2, 7 and 8, and no specific examples of nucleic acids that are "substantially identical" to them. The Examiner further argues that "substantially identical" encompasses a genus of oligonucleotides that are not described in the specification and as a result one of ordinary skill in the art would not be convinced that the Applicant was in possession of the claimed genus at the time of filing.

The Applicants would like to point out that the claims were amended in response to the first office action to remove the "substantially identical" language and to add additional structural and functional limitations: 1) an "at least or about 80% identical" requirement; 2) a well defined functional requirement, i.e. that the oligo primers are capable of amplifying a particular portion of a particular Exon of *DPD* mRNA (either Exon 1 or 6, depending on the claim), and the *DPD*

mRNA is from FPE tissue; and 3) a stringent hybridization requirement. Applicants have herewith amended the claims so that the identity requirement is now recited as "at least 80%."

Applicant herewith respectfully request reconsideration of this ground of rejection. The Examiner refers to *The Regents of the University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir.1997)(hereinafter referred to as *UC v. Eli Lilly*) as a basis for the Written Description rejection. *UC v. Eli Lilly* states that a claim containing only functional limitations without structural characteristics is insufficient to satisfy the Written Description requirement. The situation in *UC v. Eli Lilly* is not present in the subject application, since the present claims have been amended to include two structural characteristics (i.e. percent identity and stringent hybridization requirements, as well as a functional limitation (i.e. capable of amplifying a specified portion of *DPD* mRNA isolated from fixed and paraffin embedded (FPE) tissue).

Further, the United States Court of Appeals for the Federal Circuit, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002)(hereinafter referred to as *Enzo*), has further clarified the Written Description requirement and provided more guidance. In characterizing its earlier case of *UC v. Eli Lilly*, the Court in *Enzo* noted that the written description was not met as "the specification and generic claims to all cDNAs encoding for vertebrate or mammalian insulin did not describe the claimed genus because they did not set forth any common features possessed by members of the genus that distinguished them from others." *Enzo*, 296 F.3d at 1327. Unlike the case in *UC v. Eli Lilly*, in the present application, the claims set forth common features possessed by members of the genus that distinguishes them from others. The claims set forth the common feature that all of the claimed oligonucleotide primers must be capable of performing a very specifically defined function, in addition to having at least 80% identity and hybridize under stringent conditions (which is defined in the specification as what one in the art would consider "highly stringent conditions"). Thus, applicants respectfully submit that the shortcomings found in the claims at issue in *UC v. Eli Lilly*, are not present in the subject claims.

Applicants respectfully also submit that the Written Description Guidelines provide

guidance of the Written Description requirements. Example 9 of the Written Description Guidelines (Federal Register, Vol. 66, No. 4, Friday, January 5, 2001), states that:

> [A] person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because highly stringent conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, **since highly stringent hybridization conditions *in combination* with the coding function of DNA** and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

(emphasis added).

Thus, it appears that the Guidelines reveal that the written description requirement would be met by claims reciting high stringent hybridization conditions in combination with a functional requirement. In addition, to discussing *UC v. Eli Lilly*, the Court in *Enzo* noted that the PTO "has determined that such claims may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar," citing Example 9 of the Guidelines at 35-37. *Enzo*, 296 F.3d at 1327. Further, the Court stated that "it is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo*, 296 F.3d at 1324. The Court further quoted the Guidelines referenced above: "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics. . .i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" The Federal Circuit thereafter stated that it is "persuaded by the Guidelines" and "adopts the PTO's standard for determining compliance with the written description requirement." *Enzo*, 296 F.3d at 1325.

As such, the Applicant respectfully submits that the amended claims at issue meet the written description requirement as they recite both a functional requirement (capable of amplifying a specified portion of *DPD* mRNA from FPE tissue) and several structural

requirements (stringent hybridization conditions as clearly defined in the specification and understood to be high stringent conditions by one skilled in the art) and a percent identity requirement.

For further guidance, the Federal Circuit stated in *Enzo* that the specification and claims at issue in *Enzo* would meet the written description requirement "if the **functional characteristic** of preferential binding to N. gonorrhoeae over N. meningitidis were coupled with a disclosed **correlation between that function and a structure** that is sufficiently known or disclosed." (emphasis added). *Enzo*, 296 F.3d at 1324-25. The claims of the subject application recite functional characteristic (capable of amplifying certain exons of *DPD* mRNA from FPE tissue) coupled to a structure that is sufficiently known or disclosed (at least 80% identity and hybridizes under stringent conditions to a complement of the enumerated SEQ ID NO.). Accordingly, Applicant submits that the application and the claims satisfy the 112, first paragraph written description requirement. Withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 6-11, 17-22, and 26 under 35 U.S.C. § 103 (a) as allegedly being unpatentably obvious over Gonzales *et al.*, U.S. Patent No. 6,015,673 in view of Willhauck *et al.*, BioTechniques, 1998, 25:655-659. The Examiner opines that SEQ ID NO: 5 of Gonzales *et al.* teaches an oligonucleotide with 14 of 19 nucleotides identical to claimed SEQ ID NO: 1. The Examiner further alleges that such an oligonucleotide is 73% identical with claimed SEQ ID NO: 1.

Claim 6 has been amended to recite that the oligonucleotide is at least 80% identical to SEQ ID. NO: 1. Accordingly, applicants submit that this ground of rejection is moot as Gonzales' oligonucleotide is not at least 80% identical to SEQ ID No:1. Further, there is no teaching nor suggestion that the Gonzales nucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2.

Although, on its face, it appears that Gonzales *et al.'s* RTF1 and RTR1 may be useful for amplifying a 1.5kb *DPD* cDNA fragment, there is nothing in Gonzales *et al.* that would suggest to one of skill in the art that either RTR1 nor the allegedly anticipatory RTF1, either together or individually, would be appropriate for amplifying mRNA isolated from fixed and paraffin embedded tissue. Therefore, one of skill in the art would not be motivated to modify either RTF1 or RTR1, let alone search for or design a purified oligonucleotide consisting of the sequence of SEQ ID NO: 1, or a sequence which is at least 80% identical therewith and hybridizes to a complement of SEQ ID NO: 1 under stringent conditions; wherein the isolated and purified oligonucleotide is capable of amplifying a portion of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2, as claimed. Accordingly, it can further be concluded that Gonzales *et al.* cannot be asserted to suggest or contemplate the claimed oligonucleotides either.

Moreover, even if one of skill in the art was motivated to draw on the teachings of Willhauck *et al.*, the combination of these references does not render the claims unpatentably obvious because, even together, they do not teach, suggest nor contemplate an oligonucleotide consisting of the sequence of SEQ ID NO: 1, or a sequence which is at least 80% identical therewith and hybridizes to SEQ ID NO: 1 under stringent conditions; wherein the isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2.

In view of the remarks and amendments made herein, Applicant respectfully asserts that the rejection is traversed, and withdrawal thereof is respectfully requested.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments. Applicants believe the claims are in condition for allowance and earnestly request a Notice of Allowance. If any extension of time is necessary for the filing of this Amendment and Reply, a petition is hereby

petitioned under 37 C.F.R. § 1.136(a), and any other fees required therefore (and any other fees) are hereby authorized to be charged to our Deposit Account No. 11-0600.

If a communication by the Examiner is necessary to expedite prosecution, the Examiner is encouraged to contact the attorney listed below or Thomas Haag at 202-220-4322.

Respectfully submitted,

KENYON & KENYON

Date: 1/24/03

Teresa Lavenue
(Reg. No. 47,737)

1500 K Street, N.W.
Washington, D.C. 20005
Telephone: (202) 220-4258
Facsimile: (202) 220-4201

VERSION WITH MARKINGS TO SHOW CHANGES MADE

6. (Twice Amended) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising:

(a) obtaining a tumor sample from a patient;

(b) isolating mRNA from said tumor sample;

(c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer having the sequence of SEQ ID: 1, or an oligonucleotide primer at least [or about] 80% identical therewith and hybridizes to a complement of SEQ ID NO: 1 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 2,

and;

an oligonucleotide having the sequence SEQ ID: 2 or an oligonculeotide primer at least [or about] 80% identical therewith and hybridizes to a complement of SEQ ID NO: 2 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of the 5' untranslated region and Exon 1 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 1;

(d) comparing the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA from step (c) to an amount of mRNA of an internal control gene.

17. (Twice Amended) A method of determining the relative level of *Dihydropyrimidine dehydrogenase* (*DPD*) gene expression in a tissue sample comprising;

(a) obtaining a tumor sample from a patient;

(b) isolating mRNA from said tumor sample;

(c) determining the amount of *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA by amplifying the mRNA using an oligonucleotide primer having the sequence of SEQ ID: 7, or an oligonucleotide primer at least [or about] 80% identical therewith and hybridizes to a complement of SEQ ID NO: 7 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 8,

and;

an oligonucleotide having the sequence SEQ ID: 8 or an oligonculeotide primer at least [or about] 80% identical therewith and hybridizes to a complement of SEQ ID NO: 8 under stringent conditions; wherein said isolated and purified oligonucleotide is capable of amplifying a portion of Exon 6 of a *Dihydropyrimidine dehydrogenase* (*DPD*) mRNA isolated from fixed and paraffin embedded (FPE) tissue when used with SEQ ID NO: 7;

(d) comparing the amount of the mRNA from step (c) to an amount of mRNA of an internal control.